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Date:	November 13, 2008
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Subject:	Overall Post-marketing Adverse Event Analysis
Drug Name(s):	Invega
Application Type/Number:	NDA- 21999
Applicant/sponsor:	Ortho McNeil Janssen
OSE RCM #:	2008-1394

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1 INTRODUCTION

Paliperidone is an atypical antipsychotic indicated for the acute and maintenance treatment of schizophrenia, and received FDA approval on December 19, 2006. Based on SDI Vector One®: National (VONA), between December 2006 and August 2008, there were 737,000 paliperidone prescriptions dispensed in U.S. retail pharmacies. Since this is a new molecular entity, DPV self-initiated this overview of adverse events reported with paliperidone in order to proactively identify any new potentially significant, serious adverse events. Paliperidone is the major active metabolite of risperidone, another atypical antipsychotic; therefore, we would expect the safety profile for both drugs to be very similar.

2 MATERIAL REVIEWED

2.1 AERS AND DATAMINING

In September 2008, DPV performed searches of the FDA's Adverse Event Reporting System (AERS) database and conducted a datamining query using WebVDME. We reviewed the 50 most frequently reported MedDRA Preferred Terms (PT), the 20 most frequently reported PTs with death as an outcome, and the OSE designated medical events (DME) reported for paliperidone. A Designated Medical Event is an event that is inherently serious and often drug-related. OSE created the DME list for working purposes; it has no regulatory significance. The data mining query results included all the adverse events with an EB05 $\geq$ 2.0 and a drug interaction search. All the results from the AERS search and datamining query can be found in the appendix 1. In section 3.1, we provide a review of unlabeled adverse events coded with an outcome of death and unlabeled DMEs.

2.2 DRUG USE DATA

In addition, a drug use analysis was performed. Year 2007 wholesales data indicate that approximately 75% of Invega® tablets were distributed into the outpatient retail pharmacy setting (data not provided).[1] We examined outpatient retail pharmacy utilization pattern from December 2006 through August 2008. Outpatient retail pharmacy settings include chain, independent, and food stores with pharmacies. Utilization from mail order pharmacies (<3% of sales) was not included in this analysis. We examined total dispensed prescriptions stratified by age, gender, and prescriber specialty using SDI Vector One®: National (VONA). To examine the diagnoses associated with a mention of Invega®, we obtained prescribing physician survey data from SDI's Physician Drug and Diagnosis Audit (PDDA). We examined the projected number of patients who filled a prescription for Invega® at a U.S. retail pharmacy using SDI Vector One®: Total Patient Tracker (TPT). Database descriptions can be found in Appendix 2.

3 RESULTS

3.1 AERS ANALYSIS

As of September 15, 2008, the AERS database contained 1,246 post-marketing adverse event reports associated with the use of paliperidone. The data presented here are crude counts, and as such, duplicates have not been reconciled. Of 1,246 reports, 1,069 were domestic and 177 were foreign, which included 636 females and 513 males with 97 reports of unknown gender. The age

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1 IMS health, IMS Nationals Sales Perspectives™, Data Extracted October 2008, source file: 0810inv.dvr

range among the 1,246 reports was 2 to 88 years with a median of 24 years. The number of adverse events reported was similar among males and females and the age group with the highest number of adverse events reported was 31 to 40 years old. (Please see appendix 1, sections 6.3.4 through 6.3.6 for the labeling status of each Preferred Term identified in the searches)

Top 50 Preferred Terms *(see Appendix 1, Section 6.3.4)*

A majority (30/50, 60%) of the top 50 Preferred Terms reported in association with paliperidone use were labeled events and two of the remaining 20 unlabeled Preferred Terms (psychotic disorder and schizophrenia) were not applicable because they were related to indications for the drug. The remaining 18 Preferred Terms were either a known symptom of the condition being treated or did not appear to be a serious adverse event requiring labeling enhancements at this time.

Top 20 Preferred Terms with Death as an Outcome *(see Appendix 1, Section 6.3.6)*

Among the 1,246 post-marketing adverse event reports associated with paliperidone, 53 were coded with an outcome of death. There were 14 cases with unlabeled events that reported an outcome of death; these cases are summarized below. The following cases were identified as duplicates, and are described together: cases of abasia (an inability to walk due to impaired muscle coordination) and activities of daily living impaired, cases of alanine aminotransferase increased and aspartate aminotransferase increased, a case each of hyperhidrosis and Torsade de pointes (described under *Torsade de pointes*), and case each of pulmonary embolism and cardiac arrest (described under *cardiac arrest*). In addition, there was a duplicate of Torsade de pointes.

Cardiac disorders

Acute myocardial infarction (n=1)

A 68-year old female died after experiencing an acute myocardial infarction six days after initiating therapy with paliperidone for recurrent depressive disorder. Her relevant past medical history includes obesity, arterial hypertension, and diabetes mellitus II.

Cardiac Arrest (n=2)

The first case described a 38-year old male who experienced cardiac arrest and died four days after an increase in the dose of paliperidone, which he took for approximately two months. He had a past medical history of hypertension, and his concomitant medications included omeprazole, gabapentin, valproate semisodium, atorvastatin, and furosemide. The autopsy verified the cause of death as cardiac arrest. The second case described a 51-year old female who died from a "possible pulmonary emboli and possible cardiac arrest" within three weeks of initiating therapy with paliperidone. She had a past medical history of obesity and hypertension, and her concomitant medications included sertraline, ranitidine, triamterene/hydrochlorthiazide, carvedilol, and lisinopril. Lisinopril is labeled for an association with pulmonary embolism and cardiac arrest.

Torsade de pointes (n=1)

A 26-year old female patient experienced Torsade de pointes and seizure activity and died of cardiac failure within 11 days of initiating therapy with paliperidone. Her relevant past medical history included morbid obesity. The cause of death was not confirmed and it was unknown if an autopsy was performed.

Endocrine disorders

Adrenal insufficiency (n=1)

A 55-year old male was enrolled in a study to evaluate the efficacy of paliperidone. He died after experiencing acute adrenal insufficiency, suspected dilated cardiomyopathy and cachexia one month after discontinuing an eight-month therapy course of paliperidone. His relevant past medical history included hypotension, anemia, intestinal polyp, gastric ulcer, and most recent to his death, excessive alcohol use.

General disorders and administration site conditions

Hyperhidrosis (n=1)

A male patient (unknown age) experienced body stiffness and rigidity, severe muscle weakness, profuse sweating, and inability to walk, and died due to "sudden heart failure" within 10 days of initiating paliperidone. Although the report did not specifically mention neuroleptic malignant syndrome, the signs and symptoms experienced are indicative of the syndrome.

Hepatobiliary disorders

Alanine/Aspartate aminotransferase increased (n=1)

A 67-year old female experienced elevated hepatic transaminase levels one month after the discontinuation of therapy with paliperidone for schizophrenia, and died from pneumonia and multi-organ failure.

Nervous system disorders/Social circumstances

Abasia/Activities of daily living impaired (n=1)

An 83-year old female received paliperidone for 1-2 weeks for dementia related psychosis due to Alzheimer's disease. The patient experienced a decline in function and died a few weeks after the discontinuation of paliperidone.

Psychiatric disorders

Agitation (n=1)

A 68-year old male committed suicide by hanging within five months of initiating therapy with paliperidone. The report stated that the patient had thoughts of suicide years before the initiation of paliperidone.

Hallucination (auditory)(n=2)

The first case described a 58-year old male patient who experienced a sudden cardiac death three days after an increase in paliperidone dose, which he was taking for less than three weeks. His medical history included alcohol abuse, hypertension, auditory hallucinations and nicotine abuse. The second case described a 49-year old male patient who committed suicide within five months of initiating paliperidone and within the same month of initiating haloperidol for auditory hallucinations.

Respiratory disorders

Asthma (n=2)

In the first case, a 31-year old female experienced an asthma attack after installing new carpet; however, the cause of death was unknown. In the second case, a 25-year old male patient required oxygen via nasal cannula due to his history of bronchial asthma, and died from an asthma attack. Both of these patients had a past medical history of asthma and the duration of therapy with paliperidone was unknown.

Vascular disorders

Pulmonary embolism (n=1)

An elderly female (age unspecified) died from a pulmonary embolism within one month of discontinuing risperidone and initiating paliperidone.

Designated Medical Events *(see Appendix 1, section 6.3.5)*

A Designated Medical Event is an event that is inherently serious and often drug-related. OSE created the DME list for working purposes; it has no regulatory significance. The search of designated medical events associated with the use of paliperidone resulted in 49 reports. We summarized nine cases with unlabeled DMEs here:

Agranulocytosis (n=3)

The first case described a female patient (unknown age) who experienced agranulocytosis within two weeks of initiating therapy with paliperidone. Her concomitant medications included chlorpromazine, divalproex sodium, and lamotrigine, which are all labeled for an association with agranulocytosis. The second case described a 28-year old male patient who experienced leukopenia and agranulocytosis two weeks after the discontinuation of paliperidone, which he took for five months. His concomitant medications included zolpidem, which is labeled for leukopenia, and lorazepam, which is labeled for agranulocytosis. The patient had not recovered at the time of reporting. The third case did not provide enough information other than reporting that the patient experienced agranulocytosis sometime after the initiation of paliperidone.

Blindness (n=1)

A 46-year old female patient who was "declared totally blind" was diagnosed with blepharospasm, damage to eye muscles, damaged eye nerves and involuntary eye blinking on the same day she initiated therapy with paliperidone. She remained on paliperidone for six months and at the time of reporting, the patient had not recovered from her condition.

Deafness (n=1)

A 46-year old female patient experienced tardive dyskinesia, neck to back spasm, flushing and chills after abruptly discontinuing therapy with paliperidone, which she had taken for almost 1&1/2 months. The patient was hospitalized due to the withdrawal dyskinesia, hyponatremia and rapid hearing loss, of which there was a family history. Her concomitant medications included venlafaxine XR, lamotrigine, bupropion XR, and gabapentin, which are all labeled for an association with deafness.

Respiratory Failure (n=2)

The first case described a 48-year old female who experienced myocardial infarction, cardiac failure, and respiratory failure within 1&1/2 months of initiating therapy with paliperidone. Her relevant past medical history included cardiac arrest, "cardiac issues", "respiratory issues", and obesity. At the time of reporting, the patient had recovered from respiratory failure. The second case described a 4-year old female who experienced a severe overdose of paliperidone resulting in coma and respiratory failure. At the time of reporting, the patient had fully recovered.

Stevens - Johnson syndrome (n=1)

A 37-year old male patient developed Stevens-Johnson Syndrome within "one to two weeks" of increasing the dose of paliperidone, which he was taking for an unknown duration. The relevant concomitant medications, which are labeled for an association with SJS, include ezetimibe/simvastatin, diltiazem, hydrochlorothiazide, and topiramate. Therapy with paliperidone was discontinued and the condition resolved on an unknown date.

Torsade de pointes + Ventricular Fibrillation (n=1)- One case described both adverse events

A 33-year old male patient was being treated with paliperidone for an unknown duration and intentionally ingested 450mg of paliperidone. As a result, he experienced ventricular fibrillation and Torsade de pointes, requiring defibrillation. The patient recovered from the events and the action taken with paliperidone was unknown.

3.2 DATA MINING ANALYSIS (*see Appendix 1, section 6.4)*

The query of the WebVDME version 6.0 for all preferred terms associated with paliperidone with an EB05 $\geq$ 2 retrieved 21 adverse events terms (see Appendix 1, section 6.4.1.1) organized by SOC and section 6.4.1.2 organized by decreasing EB05 score). The preferred term with the highest EB05 was galactorrhea, which is a labeled event. Of these 21 terms, eight were not considered a labeled event based on the current paliperidone label[2]. The reports associated with these eight terms were not reviewed, as many of them were either considered related to an indication for the product, a known symptom of the condition being treated, or did not appear to be a serious adverse event requiring labeling enhancements at this time. The system organ class (SOC) associated with the highest number of preferred terms was the nervous system, and they were all considered labeled events.

In addition, the interaction signal score (INTSS) search was conducted (see Appendix 1, section 6.4.1.3). The INTSS of greater than 1 indicates a stronger "association" (just a statistical association, not a causal association or degree of risk) between the 2 drugs and the event using the rest of the database as a background. This search did not identify any potential drug interactions associated with paliperidone using the threshold of INTSS scores > 1.

3.3 DRUG UTILIZATION ANALYSIS

Of the 12 selected antipsychotic agents studied, paliperidone accounted for approximately 1% of total dispensed prescriptions for this class from December 2006 through August 2008 (see Appendix 2, figure 1). The most commonly dispensed strength of paliperidone during the study period was the 6 mg strength (see Appendix 2, figure 2). Of the 737,000 paliperidone prescriptions dispensed during the study period, the majority of use was among those aged 41 to 50 years (26%), followed by those aged 17 to 30 years (20%). Around 9% of dispensed prescriptions were to pediatric patients aged 16 years or younger (see Appendix 2, figure 3). Dispensed prescriptions stratified by age and gender shows that the male to female ratio of overall dispensed paliperidone prescriptions and for prescriptions dispensed to patients aged 31-50 years was 1:1. However, for prescriptions dispensed to pediatric patients (aged $\leq$ 16 yrs) the male to female ratio was 7:3; for patients aged 17-30 years, the male to female ratio was 3:2; for patients aged 51-70 years, the male to female ratio was 2:3; and for patients aged 71 or older the male to female ratio was 3:7 (see Table 1, Appendix 2). Slightly more than 193,000 patients filled a prescription for paliperidone during the analysis period. The proportion of age and overall gender distribution was similar to dispensed prescriptions (see Tables 2 and 3, Appendix 2). Psychiatrists accounted for around 72% of paliperidone dispensed prescriptions during the study period. The most common diagnoses encountered in physician's office-based practices include paranoid schizophrenia (ICD-9 code 295.3), schizoaffective type (ICD-9 code 295.7), and bipolar affective NOS (ICD-9 code 296.7).

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[2] Invega® (paliperidone) package insert. Janssen, September 2008.

4 DISCUSSION/CONCLUSIONS

Paliperidone is an atypical antipsychotic and a new molecular entity, and we reviewed adverse events in the AERS database and queried datamining to identify any new safety events that may be of concern. We provided an overview of the most frequently reported events both in all reports and in reports with an outcome of death in the AERS database, in addition to the designated medical events reported with paliperidone. We found that most of the frequently reported events in all reports were either labeled, a known symptom of the condition being treated, or did not appear to be a serious adverse event requiring labeling enhancements at this time. In addition, our datamining query did not identify any potential safety issues.

We provided a hands-on analysis of unlabeled events with an outcome of death and unlabeled DMEs, and the number of events reported with most of these unlabeled events was too few to draw any significant conclusion. However, we noted that there were three cases of agranulocytosis reported with paliperidone. At the time of previous OSE review of agranulocytosis for all atypical antipsychotic[3], where we recommended that the labels of all atypical antipsychotics[4] be enhanced to include agranulocytosis in the Warnings/Precautions section, paliperidone was recently approved and not included in the review. Although these three cases did not provide laboratory values or complete details, since paliperidone is a major active metabolite of risperidone, it is biologically plausible that paliperidone would cause similar adverse events as risperidone. Agranulocytosis is known to occur with risperidone and therefore, the current paliperidone should be updated to include agranulocytosis as recommended in the previous OSE consult.

5 RECOMMENDATIONS

- We recommend enhancing the current paliperidone label to include agranulocytosis as recommended in the previous OSE consult.
- DPV will continue to monitor adverse events with paliperidone.

[3] Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.
[4] With the exception of ziprasidone, which had no cases of agranulocytosis included in the review and aripiprazole, which was already labeled.

6 APPENDIX 1

6.1 COMPLETED AND ONGOING POST-MARKETING SAFETY REVIEWS BY DIVISION OF PHARMACOVIGILANCE:

Date	Issue	Summary/Recommendations
April 29, 2008	Death	A class review of atypical antipsychotics regarding pediatric death cases. We did not identify any cases of death with paliperidone.

6.2 POTENTIAL SAFETY ISSUES

None at this time

6.3 CRUDE COUNTS OF AERS REPORTS

Duplicate reports may have been submitted for the same patient. Duplicate reports may include follow-up information from the manufacturer and/or from multiple reporters (e.g., family member, physician, pharmacist, nurse, etc.). Reported outcomes are the coded outcomes submitted to the Agency; causality and the role of the drug product in the coded outcome have not been determined for this evaluation.

AERS **crude** counts of all reports:

1246 Reports as of September 15, 2008

- AERS **crude** counts of reports coded as a **U.S. report source** = 1069
- AERS **crude** counts of reports coded as a **foreign report source** = 177
- AERS **crude** counts of reports coded as an **unknown report source** = 0

6.3.1 Reported Outcomes As Indicated On Section B.2. Of The Medwatch Form.

AERS Crude Counts of Reports for *Each* Serious Outcome:

(Note: A Report May Have More Than One Outcome Coded)

Date of AERS Search: September 15, 2008

Outcome	US	Foreign	Null	Total
Death	36	17	0	53
Hospitalization	126	83	0	209
Life-Threatening	15	10	0	25
Disability or Permanent Damage	1	3	0	4
Congenital Anomaly	0	0	0	0
Other Serious (required intervention)	163	63	0	226

6.3.2 Percentage of U.S. And Foreign Adverse Events for Each Gender

- The percentage of foreign and domestic adverse events of the NME in females and the percentage use of the NME in U.S. females (source: AERS and SDI VONA).
- The percentage of foreign and domestic adverse events of the NME in males and the percentage use of the NME in U.S. males (source: AERS and SDI VONA).

	Foreign Adverse Event reports December 19, 2006 to September 15, 2008 (n=177)	**Domestic Adverse Event reports** December 19, 2006 to September 15, 2008 (n=1069)	**Domestic Drug Use – Total Prescriptions (%)** December 1, 2006 to August 31, 2008
Female	74 (41.8%)	562 (52.6%)	363,000 (49.2%)
Male	99 (55.9%)	414 (38.7%)	364,000 (49.4%)
Unknown	4 (2.3%)	93 (8.7%)	10 (1.4%)

6.3.3 Percentage of U.S. And Foreign Adverse Events for Each Age Band

Adverse Event Reports in AERS database by Age Category

Date of AERS Search: September 15, 2008

(Crude counts, duplicates have not been reconciled)

Age Group	**Foreign Adverse Event Reports (%) from approval to September 15, 2008 (n = 177)**	**Domestic Adverse Event Reports (%)from approval to September 15, 2008 (n= 1069)**	**Domestic Drug Use – Total Prescriptions % (n=737,000)**
0 – 1 yr	0	3 (0.28%)	69,000 (*9.4%)*
2 yrs – 5 yrs	1 (0.56%)	3 (0.28%)	
6 yrs – 11 yrs	0	16 (1.5%)	
12 yrs – 16 yrs	2 (1.1%)	29 (2.7%)	
17 yrs – 20 yrs	5 (2.8%)	47 (4.4%)	148,000 (*20.1%)*
21 yrs – 30 yrs	34 (19.2%)	144 (13.5%)	
31 yrs – 40 yrs	41 (23.2%)	139 (13%)	131,000 (*17.7%)*
41 yrs – 50 yrs	29 (16.4%)	137 (12.8%)	184,000 (*24.9%)*
51 yrs – 60 yrs	20 (11.3%)	72 (6.7%)	135,000 (*18.3%)*
61 yrs – 70 yrs	13 (7.3%)	33 (3%)	43,000 (*5.9%)*
71 yrs +	2 (1.1%)	13 (1.2%)	17,000 (*2.2%)*

Unknown	31 (17.5%)	433 (40.5%)	11,000 (*1.4%)*

6.3.4 AERS Crude Counts of the Top 50 Preferred Term Adverse Events

- A report may contain more than one preferred term
- Labeling status information was obtained from the September 2008 label.

Table 1. AERS **crude** counts of the **top 50 events** for NME (counts of MedDRA preferred terms, sorted by decreasing number)

From approval to September 15, 2008

Label Location: AR= Adverse Reactions, BW=Boxed Warning, OD= Overdosage, PME= Postmarketing Experience, W/P= Warnings/Precautions

Rank	Preferred Term	Count of PTs	Percent of Total	Label Status	Label Location	Comments
1	Galactorrhoea	85	6.82	Labeled	W/P	Labeled under hyperprolactinemia
2	Extrapyramidal Disorder	58	4.65	Labeled	AR	
3	Dystonia	54	4.33	Labeled	AR	
4	Blood Prolactin Increased	53	4.25	Labeled	W/P	Labeled as hyperprolactinemia
5	Weight Increased	50	4.01	Labeled	AR	Labeled as weight gain
6	Tremor	37	2.97	Labeled	AR	
7	Akathisia	35	2.81	Labeled	AR	
8	*Insomnia*	*32*	*2.57*	*Unlabeled*		
9	Dyskinesia	29	2.33	Labeled	AR	
10	Oedema Peripheral	29	2.33	Labeled	AR	Labeled as edema only
11	Dizziness	27	2.17	Labeled	AR	
12	*Drug Ineffective*	*27*	*2.17*	*Unlabeled*		
13	Psychotic Disorder	27	2.17	N/A		Indication
14	Somnolence	26	2.09	Labeled	AR	
15	Amenorrhoea	24	1.93	Labeled	W/P	Labeled under hyperprolactinemia
16	*Anxiety*	*24*	*1.93*	*Unlabeled*		*Part of disease state*
17	Convulsion	24	1.93	Labeled	W/P	Labeled as seizures
18	Headache	24	1.93	Labeled	W/P	
19	*Aggression*	*22*	*1.77*	*Unlabeled*		*Part of disease state*
20	*Nausea*	*22*	*1.77*	*Unlabeled*		

21	*Rash*	*22*	*1.77*	*Unlabeled*		
22	*Restlessness*	*22*	*1.77*	*Unlabeled*		
23	Suicide Attempt	22	1.77	Labeled	W/P	
24	Tachycardia	22	1.77	Labeled	AR	
25	Sedation	21	1.69	Labeled	AR	Labeled as somnolence
26	Tardive Dyskinesia	21	1.69	Labeled	W/P & AR	
27	Vomiting	21	1.69	Labeled	AR	
28	Musculoskeletal Stiffness	19	1.52	Labeled	AR	
29	Neuroleptic Malignant Syndrome	19	1.52	Labeled	W/P	
30	Suicidal Ideation	19	1.52	Labeled	W/P	Labeled as suicide
31	*Breast Discharge*	*18*	*1.44*	*Unlabeled*		*Galactorrhea and blood prolactin increased are labeled*
32	Death	18	1.44	Labeled	BW & W/P	
33	*Chest Pain*	*16*	*1.28*	*Unlabeled*		
34	*Depression*	*16*	*1.28*	*Unlabeled*		
35	Drooling	15	1.20	Labeled		
36	Completed Suicide	14	1.12	Labeled	W/P	Labeled as suicide
37	Cerebrovascular Accident	13	1.04	Labeled	W/P	
38	*Diarrhoea*	*13*	*1.04*	*Unlabeled*		
39	*Dyspnoea*	*13*	*1.04*	*Unlabeled*		
40	*Hallucination, Auditory*	*13*	*1.04*	*Unlabeled*		
41	Hyperprolactinemia	13	1.04	Labeled	W/P	
42	*Mania*	*13*	*1.04*	*Unlabeled*		
43	Schizophrenia	13	1.04	N/A		Indication
44	*Agitation*	*12*	*0.96*	*Unlabeled*		
45	*Gait Disturbance*	*12*	*0.96*	*Unlabeled*		*Parkinsonism is labeled*
46	Overdose	12	0.96	Labeled	W/P	Labeled as a risk as part of suicide and the label has an overdose section
47	*Confusional State*	*11*	*0.88*	*Unlabeled*		

48	Fatigue	11	0.88	Labeled	AR	
49	Palpitations	11	0.88	Labeled	AR	
50	*Weight Decreased*	*11*	*0.88*	*Unlabeled*		

6.3.5 Designated Medical Events (DMEs) and the crude counts for each DME

A Designated Medical Event (DME) is an event that is inherently serious and often drug-related. OSE created the DME list for working purposes; it has no regulatory significance.

- The following is a table of crude counts of designated medical events (DME) associated with paliperidone adverse event reports in the AERS database. Please note that these reports have not been analyzed, therefore, causality has not been assessed, and the numbers may contain duplicated reports.
- Additionally, the terms are not mutually exclusive; one report may contain an unlimited number of preferred terms.
- Labeling status information was obtained from the September 2008 label.

Designated Medical Event Terms Reported for paliperidone

Date of AERS Search: September 22, 2008

Label Location: AR= Adverse Reactions, BW=Boxed Warning, OD= Overdosage, PME= Postmarketing Experience, W/P= Warnings/Precautions

DME Preferred Term	Total Report/ Event Count	# Serious	# Death	Label Status	Label Location	Comments
Agranulocytosis	*5*	*5*	*0*	*Unlabeled*		
Anaphylactic reaction	3	3	0	Labeled	AR	
Anaphylactoid reaction	1	1	0	Labeled		Anaphylactic reaction is labeled
Blindness	*1*	*1*	*0*	*Unlabeled*		
Convulsion	24	22	2	Labeled	W/P	Labeled as seizures
Deafness	*2*	*2*	*0*	*Unlabeled*		
Grand Mal Convulsion	4	4	0	Labeled		Seizures is labeled
Renal failure acute	2	2	0	Labeled	W/P	Labeled as part of NMS
Respiratory failure	*2*	*2*	*0*	*Unlabeled*		
Stevens Johnson Syndrome	*1*	*1*	*0*	*Unlabeled*		
Torsade de pointes	*3*	*1*	*2*	*Unlabeled*		*QT prolongation is labeled and the risk of TdP is mentioned within.*
Ventricular Fibrillation	*1*	*1*	*0*	*Unlabeled*		

6.3.6 AERS Crude Counts of the Top 20 Preferred Terms with Death as an Outcome

Date of AERS Search: September 15, 2008

Label Location: AR= Adverse Reactions, BW=Boxed Warning, OD= Overdosage, PME= Postmarketing Experience, W/P= Warnings/Precautions

Rank	Preferred Term	Count of PTs	Percent of Total	Label Status	Label Location	Comments
1	Death	18	33.96%	Labeled	BW & W/P	
2	Completed suicide	14	26.42%	Labeled	W/P	Labeled as suicide
3	*Asthma*	*2*	*3.77%*	*Unlabeled*		
4	*Cardiac arrest*	*2*	*3.77%*	*Unlabeled*		
5	Cardiac failure	2	3.77%	Labeled	BW	Labeled as heart failure
6	Convulsion	2	3.77%	Labeled	W/P	Labeled as seizures
7	*Hallucination, auditory*	*2*	*3.77%*	*Unlabeled*		
8	*Hyperhidrosis*	*2*	*3.77%*	*Unlabeled*		
9	Overdose	2	3.77%	Labeled	W/P	Labeled as a risk as part of suicide and the label has an overdose section
10	*Pulmonary embolism*	*2*	*3.77%*	*Unlabeled*		
11	*Torsade de Pointes*	*2*	*3.77%*	*Unlabeled*		*QT prolongation is labeled and the risk of TdP is mentioned within*
12	*Abasia*	*1*	*1.89%*	*Unlabeled*		*Parkinsonism is labeled*
13	*Activities of daily living impaired*	*1*	*1.89%*	*Unlabeled*		
14	*Acute myocardial infarction*	*1*	*1.89%*	*Unlabeled*		
15	*Adrenal insufficiency*	*1*	*1.89%*	*Unlabeled*		
16	*Agitation*	*1*	*1.89%*	*Unlabeled*		
17	*Alanine aminotransferase increased*	*1*	*1.89%*	*Unlabeled*		
18	Arrhythmia	1	1.89%	Labeled	AR	
19	*Aspartate aminotransferase increased*	*1*	*1.89%*	*Unlabeled*		
20	Aspiration	1	1.89%	Labeled	W/P	Labeled under dysphagia

6.4 AERS DATA MINING OVERVIEW

Data Mining Analysis: List all drug-events with an EB05 value ≥ 2.0.

Note that these data **do not**, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

- The following tables contain the same information, but are organized by 1) System Organ Class or 2) According to decreasing EB05 score
- Preferred Terms achieving a data mining score greater than or equal to 2.0 are included in the table.

6.4.1 Paliperidone Data Mining Analysis: WebVDME Data Current as of August 8, 2008

6.4.1.1 Data Mining Results for paliperidone, Organized by System Organ Class

Label Location: AR= Adverse Reactions, BW=Boxed Warning, OD= Overdosage, PME= Postmarketing Experience, W/P= Warnings/Precautions

Ingredient	PT	SOC	N	EB05	EBGM	EB95	Label Status	Label Location	Comments
Paliperidone	Hyperprolactinaemia	Endo	9	8.613	21.242	38.303	Labeled	W/P	
Paliperidone	Blood prolactin increased	Inv	41	51.677	67.363	86.598	Labeled	W/P	Labeled as hyper - prolactinemia
Paliperidone	Musculoskeletal stiffness	Musc	19	2.511	3.695	5.289	Labeled	AR	
Paliperidone	Extrapyramidal disorder	Nerv	57	15.85	19.824	24.546	Labeled	AR	
Paliperidone	Dystonia	Nerv	52	25.17	31.82	39.789	Labeled	AR	
Paliperidone	Akathisia	Nerv	34	20.605	27.597	36.346	Labeled	AR	
Paliperidone	Dyskinesia	Nerv	27	4.455	6.274	8.86	Labeled	AR	
Paliperidone	Sedation	Nerv	21	6.16	10.542	16.561	Labeled	AR	
Paliperidone	Neuroleptic malignant syndrome	Nerv	17	4.321	7.072	12.336	Labeled	W/P	
Paliperidone	Drooling	Nerv	14	13.335	21.706	33.494	Labeled	AR	
Paliperidone	Tardive dyskinesia	Nerv	14	3.048	4.838	7.526	Labeled	W/P	
Paliperidone	Psychotic disorder	Psych	26	3.5	4.881	6.687	N/A		Indication
Paliperidone	*Restlessness*	*Psych*	*21*	*3.115*	*4.508*	*6.375*	*Unlabeled*		
Paliperidone	*Mania*	*Psych*	*13*	*2.251*	*3.593*	*5.515*	*Unlabeled*		*Indication*
Paliperidone	Schizophrenia	Psych	12	5.731	13.574	24.424	N/A		Indication
Paliperidone	*Hallucination, auditory*	*Psych*	*11*	*2.196*	*3.655*	*5.817*	*Unlabeled*		
Paliperidone	*Catatonia*	*Psych*	*7*	*2.785*	*7.097*	*21.886*	*Unlabeled*		
Paliperidone	*Disturbance in social behaviour*	*Psych*	*5*	*2.158*	*7.066*	*30.458*	*Unlabeled*		
Paliperidone	Galactorrhoea	Repro	82	92.732	111.635	133.463	Labeled	W/P	Labeled under hyper-

									prolactinemia
Paliperidone	Amenorrhoea	Repro	23	4.682	6.977	10.732	Labeled	W/P	Labeled under hyper-prolactinemia
Paliperidone	*Breast discharge*	*Repro*	*5*	*2.16*	*7.087*	*30.535*	*Unlabeled*		

6.4.1.2 Data Mining Results for paliperidone, Organized Decreasing EB05 Score

Label Location: AR= Adverse Reactions, BW=Boxed Warning, OD= Overdosage, PME= Postmarketing Experience, W/P= Warnings/Precautions

Ingredient	PT	SOC	N	EB05	EBGM	EB95	Label Status	Label Location	Comments
Paliperidone	Galactorrhoea	Repro	82	92.732	111.635	133.463	Labeled	W/P	Labeled under hyper-prolactinemia
Paliperidone	Blood prolactin increased	Inv	41	51.677	67.363	86.598	Labeled	W/P	Labeled as hyper-prolactinemia
Paliperidone	Dystonia	Nerv	52	25.17	31.82	39.789	Labeled	AR	
Paliperidone	Akathisia	Nerv	34	20.605	27.597	36.346	Labeled	AR	
Paliperidone	Extrapyramidal disorder	Nerv	57	15.85	19.824	24.546	Labeled	AR	
Paliperidone	Drooling	Nerv	14	13.335	21.706	33.494	Labeled	AR	
Paliperidone	Hyperprolactinaemia	Endo	9	8.613	21.242	38.303	Labeled	W/P	
Paliperidone	Sedation	Nerv	21	6.16	10.542	16.561	Labeled	AR	
Paliperidone	Schizophrenia	Psych	12	5.731	13.574	24.424	N/A		Indication
Paliperidone	Amenorrhoea	Repro	23	4.682	6.977	10.732	Labeled	W/P	Labeled under hyper-prolactinemia
Paliperidone	Dyskinesia	Nerv	27	4.455	6.274	8.86	Labeled	AR	
Paliperidone	Neuroleptic malignant syndrome	Nerv	17	4.321	7.072	12.336	Labeled	W/P	
Paliperidone	Psychotic disorder	Psych	26	3.5	4.881	6.687	N/A		Indication
Paliperidone	*Restlessness*	*Psych*	*21*	*3.115*	*4.508*	*6.375*	*Unlabeled*		
Paliperidone	Tardive dyskinesia	Nerv	14	3.048	4.838	7.526	Labeled	W/P	
Paliperidone	*Catatonia*	*Psych*	*7*	*2.785*	*7.097*	*21.886*	*Unlabeled*		
Paliperidone	Musculoskeletal stiffness	Musc	19	2.511	3.695	5.289	Labeled	AR	
Paliperidone	*Mania*	*Psych*	*13*	*2.251*	*3.593*	*5.515*	*Unlabeled*		*Indication*
Paliperidone	*Hallucination, auditory*	*Psych*	*11*	*2.196*	*3.655*	*5.817*	*Unlabeled*		
Paliperidone	*Breast discharge*	*Repro*	*5*	*2.16*	*7.087*	*30.535*	*Unlabeled*		
Paliperidone	*Disturbance in social behaviour*	*Psych*	*5*	*2.158*	*7.066*	*30.458*	*Unlabeled*		

6.4.1.3 INTSS scores >1 for the 3D data mining analysis

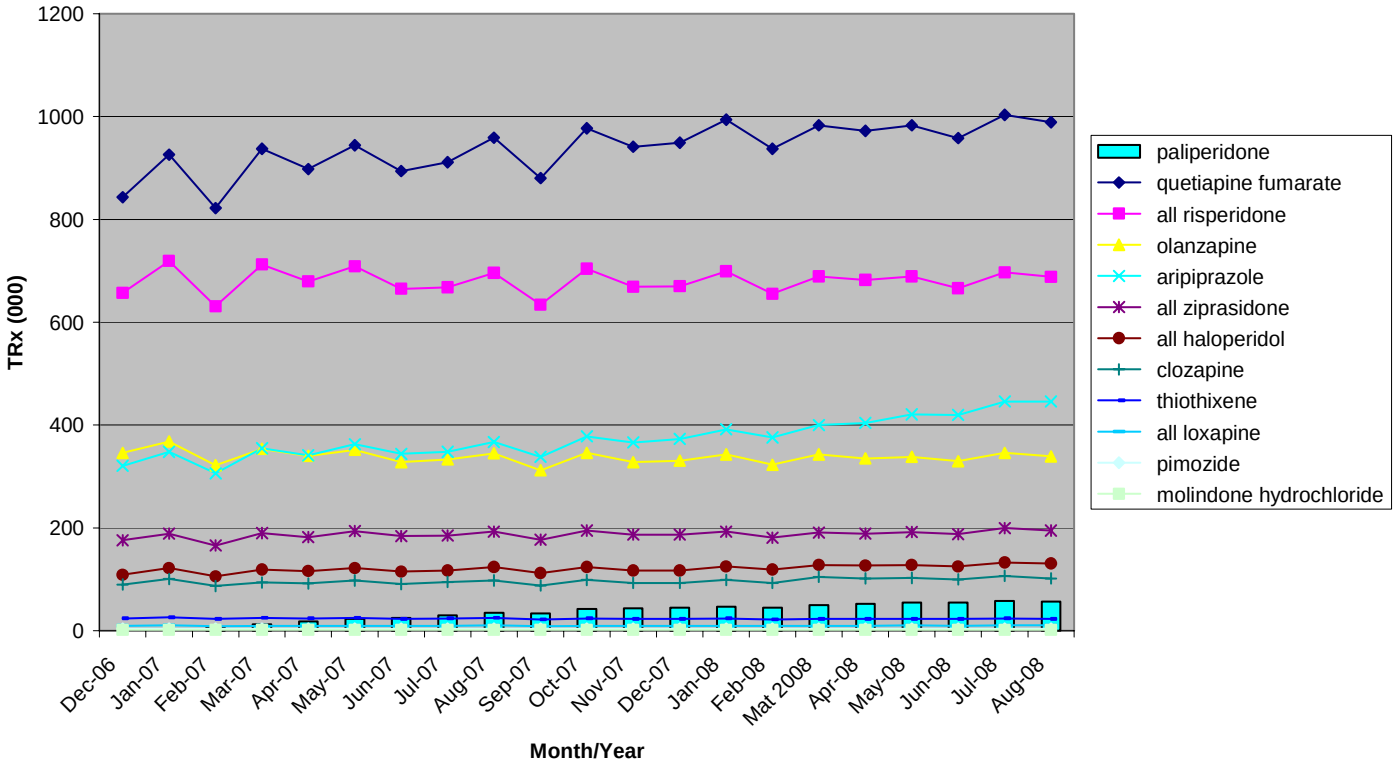
List Ingredient specific to paliperidone—any ingredient—and the "drug interaction" PT combination. [Run Ingredient 3D (S + C)]

No interactions identified

7 APPENDIX 2: DRUG USAGE DATA

7.1 DISPENSED PRESCRIPTIONS AND COMPARATORS

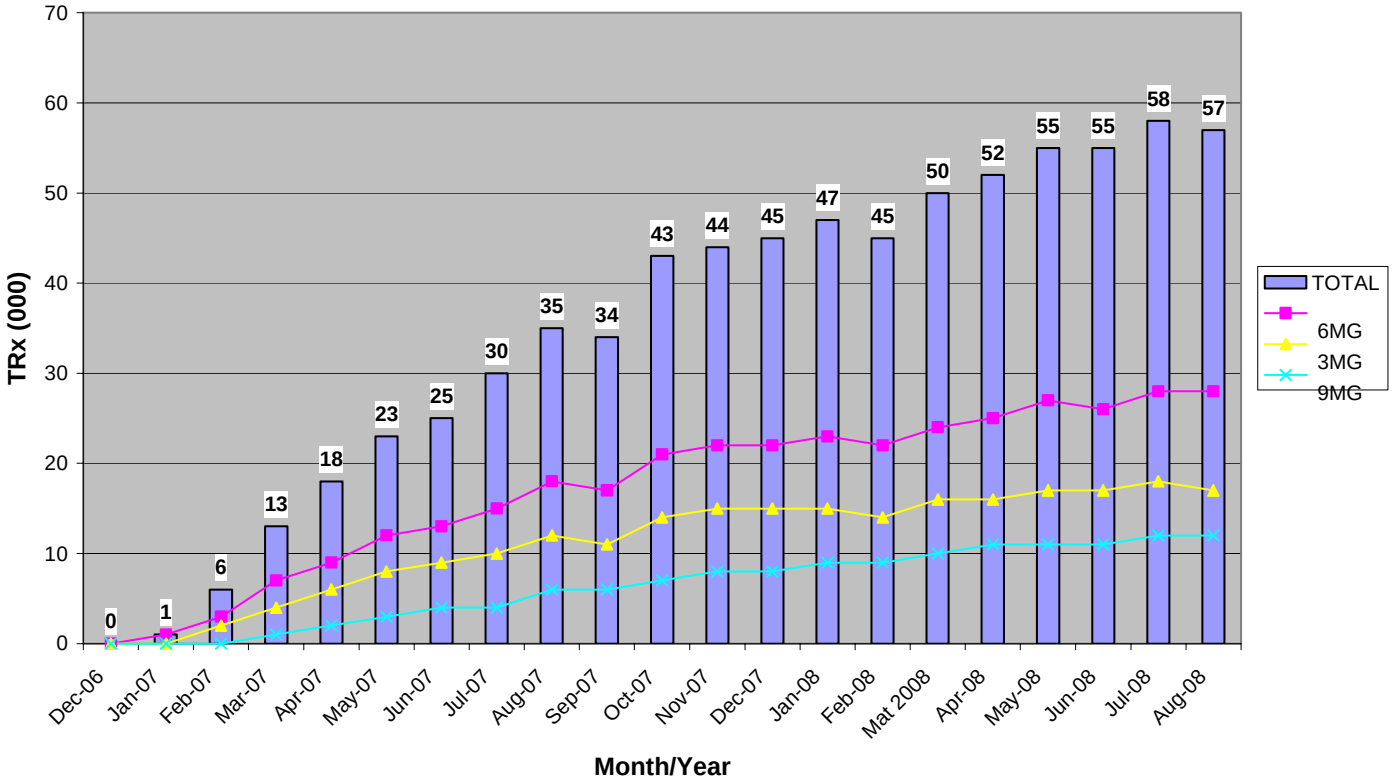
Figure 1: Total U.S. Retail Dispensed Prescriptions (In Thousands) for Paliperidone and other Select Antipsychotic Agents, Dec06-Aug08



SDI Vector One: VONA. Data extracted 10-20-08. File: 2008-1394 VONA 10-20-08 Invega comparators

7.2 DISPENSED PRESCRIPTIONS BY STRENGTH

Figure 2: Total U.S. Retail Dispensed Prescriptions (In Thousands) for Paliperidone by strength, Dec06-Aug08

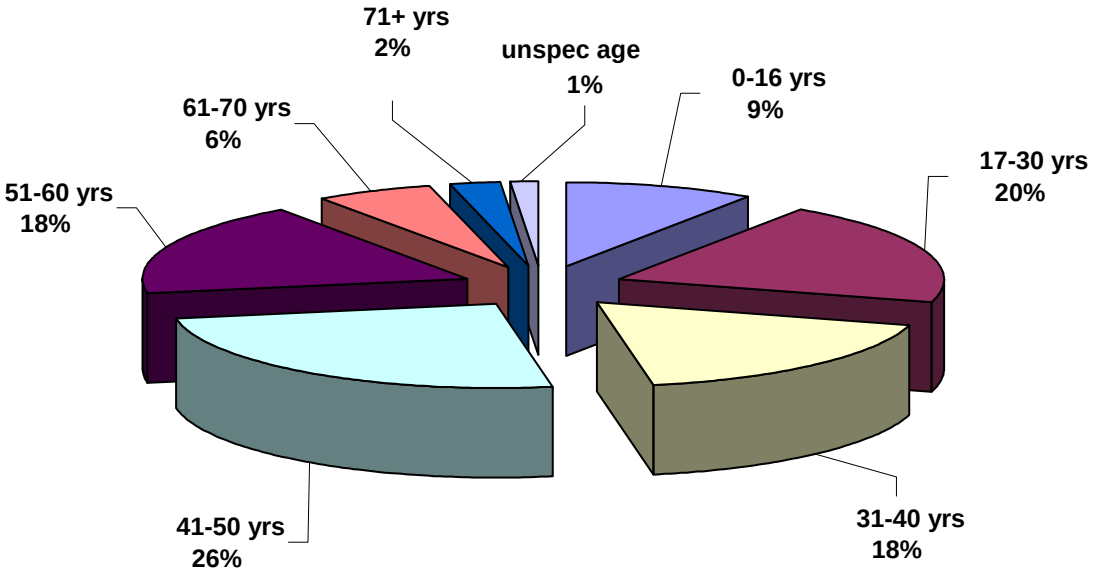


SDI Vector One: VONA. Data extracted 10-20-08. File: 2008-1394 VONA 10-20-08 Invega strength

7.3 DISPENSED PRESCRIPTIONS BY AGE

Figure 3. Proportion of Dispensed Paliperidone Prescriptions Stratified by Age, Dec06-Aug08

SDI Vector One: VONA. Data extracted 10-20-08. File:2008-1394 VONA 10-20-08 Invega age.qry



7.4 DISPENSED PRESCRIPTIONS BY AGE AND GENDER

Table 1. Paliperidone Prescriptions (In thousands) Dispensed from U.S. Retail Pharmacies stratified by age and gender, Dec06-Aug08

	Total		Male			Female			UNSPEC.		
	Retail TRxs (000)	*Share %*	Retail TRxs (000)	*Share %*	*Horiz Shr%*	Retail TRxs (000)	*Share %*	*Horiz Shr%*	Retail TRxs (000)	*Share %*	*Horiz Shr%*
paliperidone	**737**	*100.0%*	**364**	*100.0%*	***49.4%***	**363**	*100.0%*	***49.2%***	**10**	*100.0%*	*1.4%*
0-16	**69**	***9.4%***	**48**	*13.2%*	*69.7%*	**21**	*5.7%*	*29.6%*	**1**	*4.8%*	*0.7%*
17-30	**148**	*20.1%*	**89**	*24.3%*	*59.8%*	**59**	*16.1%*	*39.5%*	**1**	*10.5%*	*0.7%*
31-40	**131**	*17.7%*	**64**	*17.7%*	*49.3%*	**66**	*18.1%*	*50.3%*	**1**	*5.6%*	*0.4%*
41-50	**184**	*24.9%*	**84**	*23.0%*	*45.6%*	**99**	*27.3%*	*53.9%*	**1**	*9.1%*	*0.5%*
51-60	**135**	*18.3%*	**57**	*15.6%*	*42.0%*	**77**	*21.3%*	*57.5%*	**1**	*5.8%*	*0.5%*
61-70	**43**	*5.9%*	**15**	*4.1%*	*34.6%*	**28**	*7.8%*	*65.1%*	**0**	*1.2%*	*0.3%*
71+	**17**	*2.2%*	**4**	*1.2%*	*26.2%*	**12**	*3.3%*	*72.0%*	**0**	*2.8%*	*1.8%*
UNSPEC.	**11**	*1.4%*	**3**	*0.8%*	*28.0%*	**1**	*0.4%*	*13.2%*	**6**	*60.1%*	*58.9%*

SDI Vector One: VONA. Data extracted 10-20-08. File:2008-1394 VONA 10-20-08 Invega age and gender.qry

7.5 PATIENTS BY AGE

Table 2. Projected Number of Patients who filled an Invega Prescription at a U.S. Retail Pharmacy stratified by age, Dec06-Aug08

Product Brand	Custom Age Group	Projected Patient Count (N)	Total Patient Share (%)
INVEGA	**All**	**193,246**	**100.0%**
	0 - 16	17,193	*8.9%*
	17 - 30	43,123	*22.3%*
	31 - 40	37,475	*19.4%*
	41 - 50	48,288	*25.0%*
	51 - 60	33,213	*17.2%*
	61 - 70	11,095	*5.7%*
	71 - 85	4,465	*2.3%*
	UNKNOWN AGE	6,136	*3.2%*

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.

SDI Total Patient Tracker, data extracted 10-20-08. File: 2008-1394 TPT 10-20-08 Invega age.xls

7.6 PATIENTS BY GENDER

Table 3. Projected Number of Patients who filled an Invega Prescription at a U.S. Retail Pharmacy stratified by gender, Dec06-Aug08

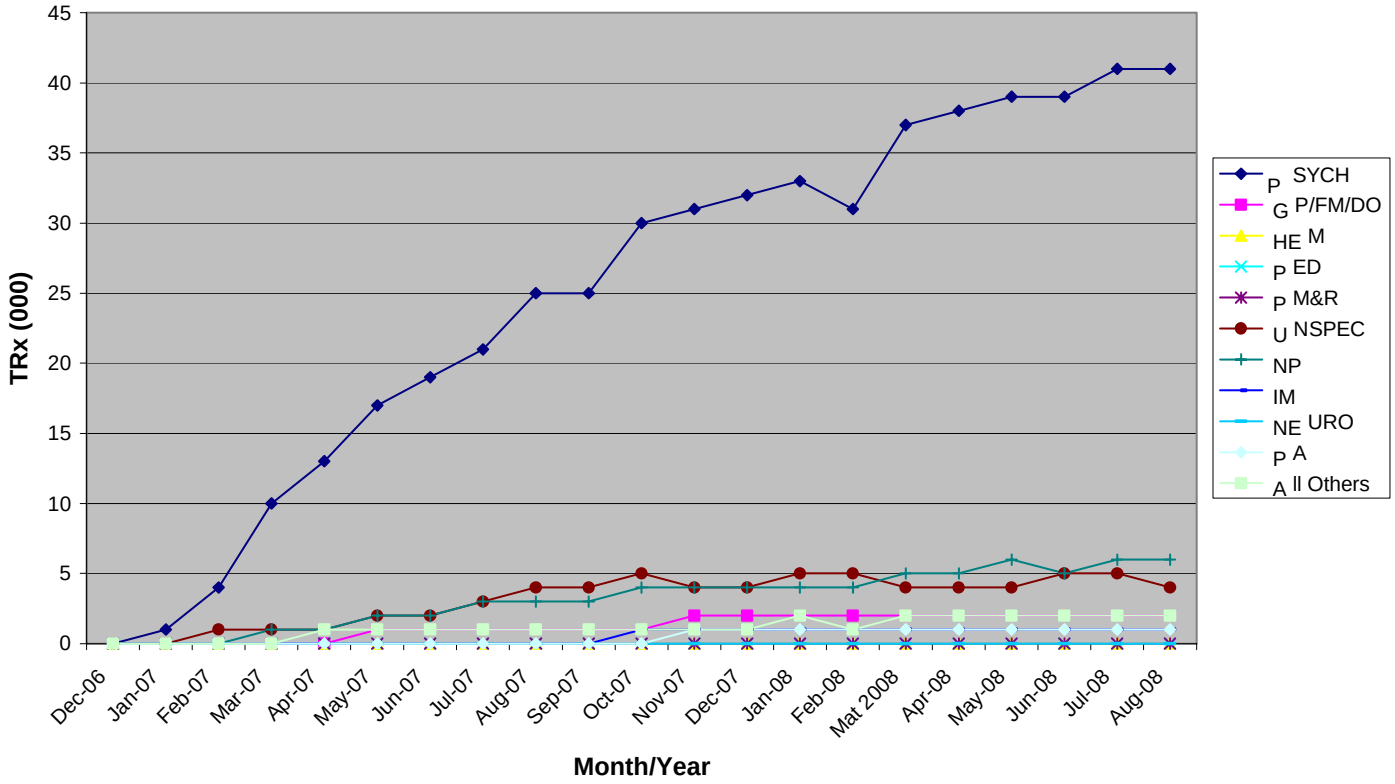
	Projected Patient Count (N)	Total Patient Share (%)
Total	**193,246**	**100.0%**
Male	91,534	*47.4%*
Female	99,021	*51.2%*

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.

SDI Total Patient Tracker, data extracted 10-20-08. File: 2008-1394 TPT 10-20-08 Invega gender.xls

7.7 PRESCRIPTIONS BY PRESCRIBER SPECIALTY

Figure 4. Dispensed Paliperidone Prescriptions (In thousands) by Prescribing Specialty, Dec06-Aug08



SDI Vector One: VONA. Data extracted 10-20-08. File: 2008-1394 VONA 10-20-08 Invega specialty.qry

7.8 INDICATIONS ASSOCIATED WITH USE

Table 4. Most Common Indications Associated with the Use* of Invega (In Thousands) in Office-Based Practice settings, Dec06-Aug08

	Uses (000)	Share %
Invega	872	100.0%
2953 PARANOID SCHIZOPHRENIA	185	21.2%
2957 SCHIZOAFFECTIVE TYPE	137	15.7%
2967 BIPOLAR AFFECTIVE NOS	102	11.6%
2959 SCHIZOPHRENIA NOS	86	9.9%
2968 MANIC-DEPRESSIVE NEC/NOS	63	7.2%
All Others	299	34.3%

*Projected Uses for a product linked to a diagnosis. The projecte number of times a product has been reported for treatment of a particular disease. A prescription was not necessarily generated but the drug was mentioned during the office visit.

Source: SDI Physician Drug and Diagnosis Audit, Dec06-Aug08, data extracted 10-20-08.
File: 2008-1394 PDDA 10-20-08 paliperidone 4ddx.qry

7.9 DATABASE DESCRIPTIONS

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI: Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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